

## REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-47 are pending in this application.

Claim 26 has been amended to correct a typographical error omitting the word "is."

Claims 11-13 and 29 have been amended to properly refer to "IPN nanoparticles."

### **I. Claim Rejections under 35 USC §112**

The Examiner has rejected Claims 11-13 on the grounds that there is insufficient antecedent basis for the term "wherein the mono-disperse nanoparticles...", and Claim 29 on the grounds that there is insufficient antecedent basis for the term "...the mono-dispersed IPN...."

Applicants have amended Claims 11-13 to recite "wherein the IPN nanoparticles..." and Claim 29 has been amended to recite "...the IPN nanoparticles...." These claims are therefore proper and in condition for allowance.

### **II. Claim Rejections under 35 USC §102**

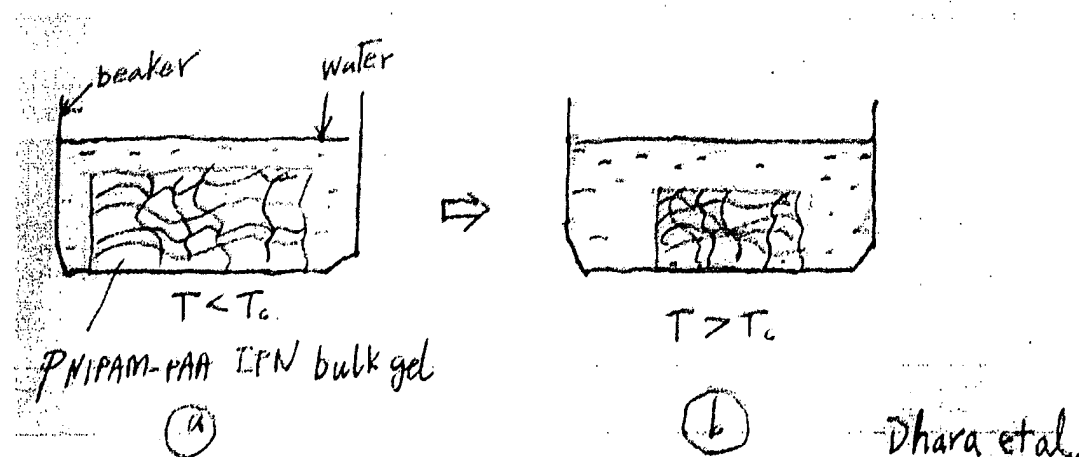
Applicants wish to thank the Examiner for withdrawing the rejection of Claims 1-10 as being anticipated by the Kubota et al. (Journal of Applied Polymer Science, 2001, Vol. 80, p. 789-805, "the Kubota Reference").

The Examiner has rejected Claims 1, 4-10, and 13-14 under 35 USC §102(b) as being anticipated by Dhara et al. (Macromol Chem Phys 2001, Vol. 202, p.3617-3623, "the Dhara Reference"). The Examiner states that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network nanoparticles wherein each

IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network; and an aqueous medium, the first polymer comprises poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), the total polymer concentration is 2 wt%, the weight ratio is 2:1 (p. 3618, first column, second and third paragraphs). The Examiner states that the hydrogel can undergo a reversible gelation in response to a change in stimulus applied thereon, the stimulus is a change in temperature, and the temperature is about 34 °C (p. 8618, second column, second and third paragraphs).

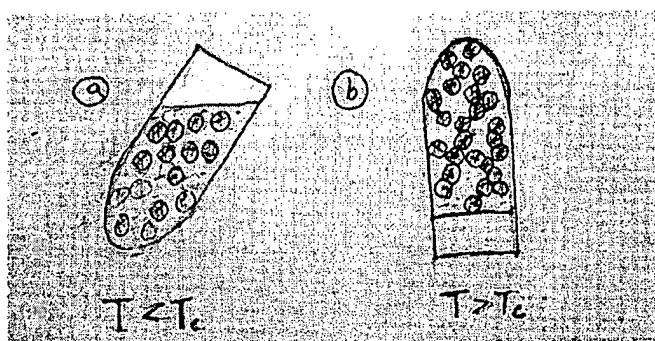
Applicants respectfully disagree with the Examiner. The hydrogel of the Dhara Reference cannot undergo a reversible gelation, as the Examiner has suggested. It can only undergo a volume phase transition (VPT). The following schematics show the difference between gelation (Schematic 2) of the currently-claimed dispersion of IPN nanoparticles and the volume phase transition (Schematic 1) of the hydrogel of the Dhara Reference.

Schematic 1 illustrates the data presented in Figure 1 page 3619 of the Dhara Reference. As the hydrogel of the Dhara Reference is immersed in water in a beaker, at pH <4.5, the hydrogel swells in water below about 34°C but shrinks above 34°C. This is called the volume phase transition (VPT) (page 3617, column 1, Dhara et al. paper).



Schematic 1

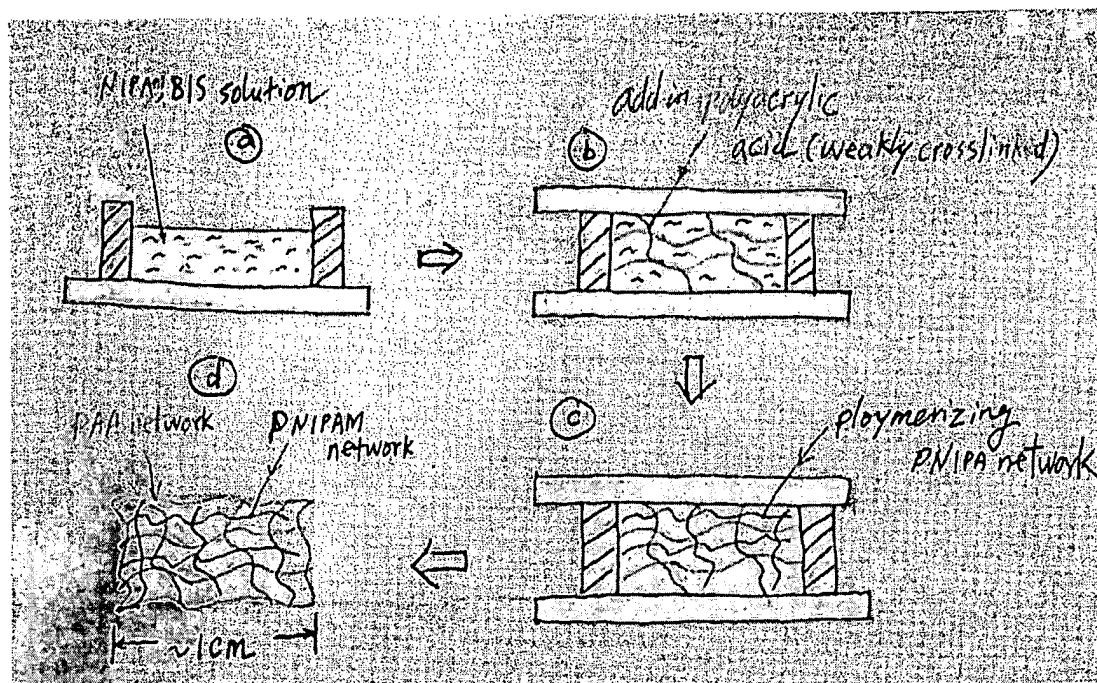
In contrast, the current claims describe a situation where millions of nanoparticles of PNIPAM-PAAc interpenetrating polymer networks were immersed in water at pH 6.5. These particles are non-sticky below 33°C but become sticky at above 33°C. As a result, below 33°C, the nanoparticle-water mixture (called a dispersion) is a fluid (Schematic 2a) but becomes a gel at above 33°C (all IPN nanoparticles stick together to form a network) (Schematic 2b). Water is contained inside every IPN nanoparticle and also contained between the nanoparticles. The transition from a fluid to a gel is called gelation. Because this transition is reversible by switching temperatures, this transition is called a reversible gelation.



Schematic 2

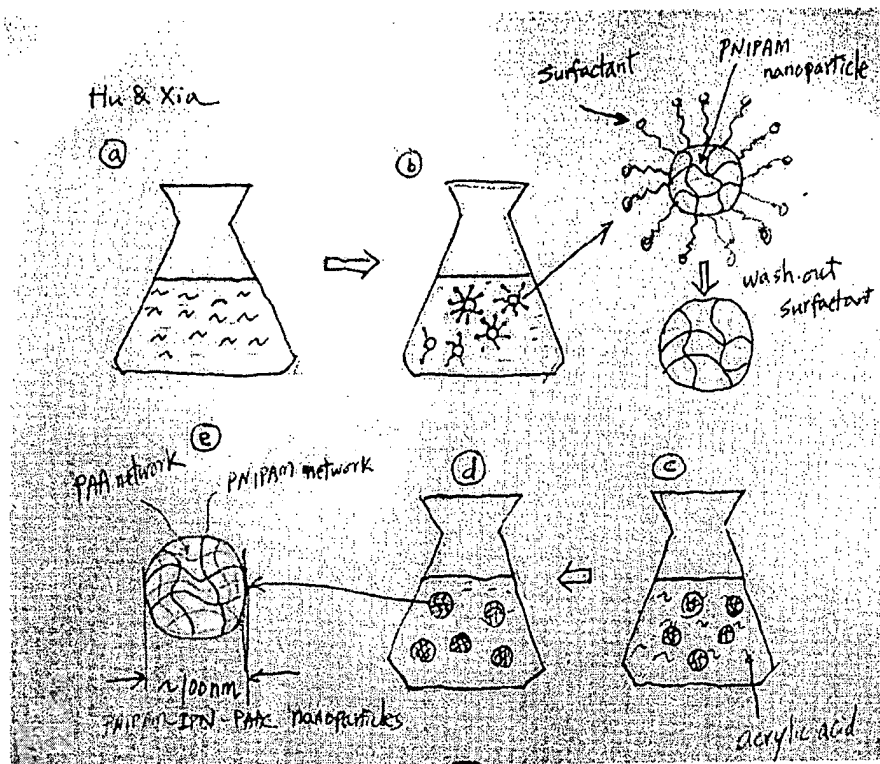
The composition of the Dhara Reference is therefore a single piece of gel below or above 34°C. This is clearly not a reversible gelation. Because the size of the hydrogel in the Dhara Reference is changed with temperature, it is called the volume phase transition.

Moreover, the method taught in the Dhara Reference cannot lead to mono-dispersed polymer nanoparticles, and the authors of the Dhara Reference did not make such a claim in their paper. It is scientifically impossible to make hydrogel nanoparticles using a gasket as a spacer. The following schematics show the difference between sample preparation according to the current claims (Schematic 4) and the Dhara Reference (Schematic 3).



Schematic 3

The Dhara Reference teaches a sample preparation (page 3618, Column 1, paragraphs 2 and 3) as in Fig. 3: (a) the first solution of NIPA, BIS, etc was placed in a glass slide and a gasket; (b) the second solution of polyacrylic acid (that is weakly crosslinked), BIS, initiator, etc, was added into the first solution, and the total solution was sealed using two glass slides with a gasket as a spacer between the two glass slides; (c) polymerization reaction took place to form the interpenetrating polymer networks (IPN) of PAAc and PNIPAM. (d) After removing glass slides and the gasket, the IPN bulk gel was immersed in water. Please note that the Dhara References does not provide information about the size of the resulting hydrogel, however, one of skill in the art would understand that since they have used a gasket as a spacer, the size of their hydrogel should be in the range of about 1 cm.



Schematic 4

This contrasts with the method taught in the current application (please see Example 1 of the specification), shown in Schematic 4: (a) NIPAM, BIS, surfactant, etc are mixed in water under nitrogen environment; (b) after an initiator is added and the temperature is increased to 70°C, the NIPAM precipitates into spheres surrounded by surfactant, and after polymerization reaction, the PNIPAM nanoparticle spheres are formed and washed to remove surfactant; (c) the PNIPAM nanoparticles are then immersed into acrylic acid, BIS, initiator water solution; (d) after polymerization of acrylic acid, nanoparticles of PNIPAM-PAA interpenetrating polymer networks (IPN) formed. The diameter of the IPN nanoparticles is about 100-200 nm.

Applicants submit that because of these differences, the Dhara Reference cannot be said to anticipate the current claims, and the claims are therefore novel and in condition for allowance.

### III. Claim Rejections under 35 USC §103

The Examiner has rejected Claims 1-47 on the grounds that they are obvious over the Dhara Reference, in view of Gan and Lyon (J. Am. Chem. Soc., 2001, Vol. 123, No. 31, p. 7511-7517, "the Gan Reference"), Hennink and Nostrum (Advanced Drug Delivery, 2002, Vol. 13, p.13-36, "the Hennink Reference"), and in further view of the Kubota Reference.

The Examiner states that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network nanoparticles, wherein each IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network, and an aqueous medium; the first polymer comprises poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), the total polymer concentration is 2 wt%, and the weight ratio is 2:1 (p. 3618, first column, second and third paragraphs). The Examiner states that the hydrogel can undergo a reversible gelation in response to a change in stimulus applied thereon, the stimulus is a change in temperature, the temperature is about 34°C (p. 8618, second column, second and third paragraphs).

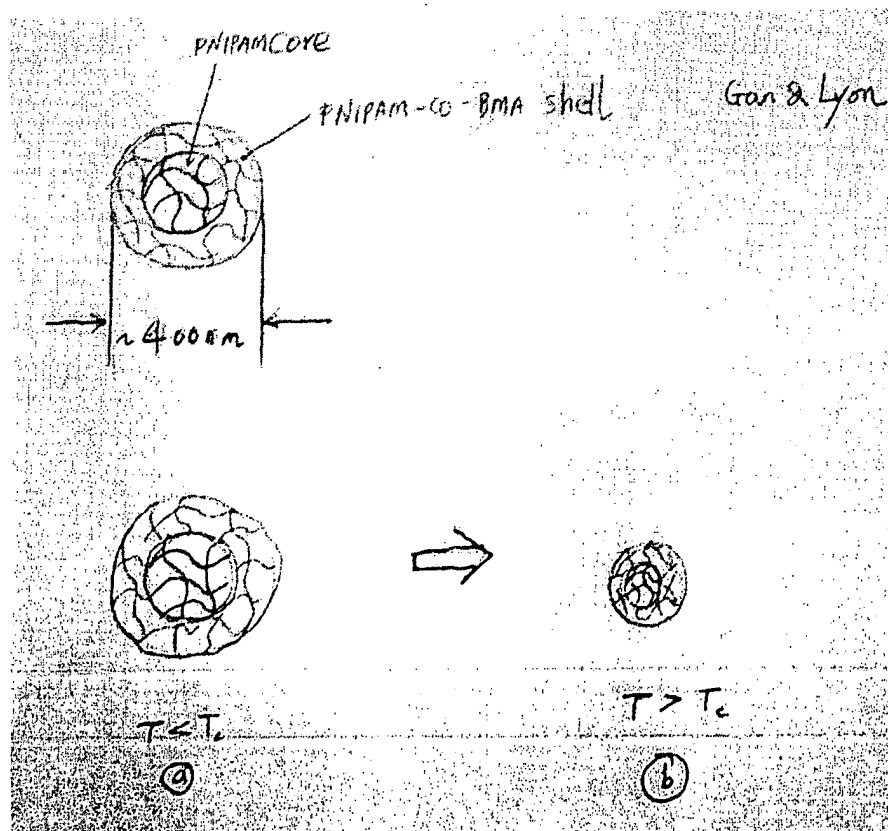
Applicants disagree with the Examiner's statement that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles. As described above, and demonstrated schematically in Schematic 3 and Schematic 4 above, Dhara's method is clearly different from the currently described methods. Specifically, the Dhara Reference teaches a method using a gasket as a spacer, which clearly does not lead to nano-range hydrogel spheres.

Moreover, by comparing Schematic 1 and Schematic 2 above, one can see that the hydrogel of the Dhara Reference is a single piece of hydrogel that undergoes the volume phase transition (VPT). That is, it has a larger size below  $T_c$  than above  $T_c$ . The currently-claimed dispersion of nanoparticles undergoes a reversible gelation: it is a fluid below  $T_c$  but becomes a gel above  $T_c$ .

The Examiner goes on to state that the Gan Reference teaches the application of hydrogel nanoparticles for drug delivery, and polymerization by mixing with SDS (surfactant). The Examiner states that the Gan Reference further teaches that the size of the particles was controlled via varying concentration of SDS during polymerization (p.7512, 2<sup>nd</sup> column line 9, and last paragraph lines 5-7).

Applicants respectfully disagree. The nanoparticles of the Gan Reference have a core-shell structure as shown in the top schematic in Schematic 5: the core is PNIPAM and the shell is either PNIPAM or PNIPAM-co-BMA (please see page 7512, 2<sup>nd</sup> column, 2 paragraph of the Gan Reference). As the temperature is increased above 34 °C, the particles shrink. (page 7514, Figure 2 of the Gan Reference). That is, the particles of the Gan Reference can have the volume phase transition (VPT) as shown in the bottom schematic in Schematic 5.

The nanoparticles of the Gan Reference have a core-shell structure and are clearly different from the currently-claimed nanoparticles that consist of PNIPAM and PAAc interpenetrating polymer networks. Because the drastic difference in the structure, the performance is also different. Specifically, the dispersion of the nanoparticles in the Gan Reference can't undergo a reversible gelation. Therefore, the teachings of the Gan Reference could not have provided information which is lacking in the Dhara Reference to lead one of skill in the art to develop the current invention.



Schematic 5

The Examiner further states that the Dhara Reference does not teach cross-linking agents EDAC and adipic acid dihydrazide. However the Examiner states that, at the time the invention was made, EDAC, a highly efficient reagent to crosslink water-soluble polymers with amide bonds, and adipic acid dihydrazide, a less toxic cross linking agent for aldehyde-mediated crosslinking of polymers, were both being used in the art as crosslinking agents for hydrogel preparation (the Hennink Reference, p. 19 column I & Fig 4., p.20, column 1).

Applicants disagree that this pertains to the present inventive step. Crosslinking agents EDAC and adipic acid dihydrazide are usually used to prepare bulk hydrogels (for example, in the Hennink Reference, p. 19, column I & Fig 4., p.20, column 1). That is, these crosslinking agents are used to link monomers to form a hydrogels. The present invention is distinct in that neighboring nanoparticles have been linked using these crosslinking agents. This has not been done in the Hennink Reference.

The Examiner further states that the Dhara Reference teaches that the incorporation of acrylic acid network imparts anionic character to the IPNs, and that PNIPA is a temperature sensitive polymer whereas PAA is pH sensitive. The Examiner states that the presence of poly (acrylic acid) (PAA) network makes the system a highly swelling hydrogel, and that the effect of PNIPA and its shrinkage above transition temperature is only observed in compositions with high PNIPA content. As PAA content increases the IPN remains uniformly swollen at all temperatures (p.3618, 2nd column, 2nd paragraph).

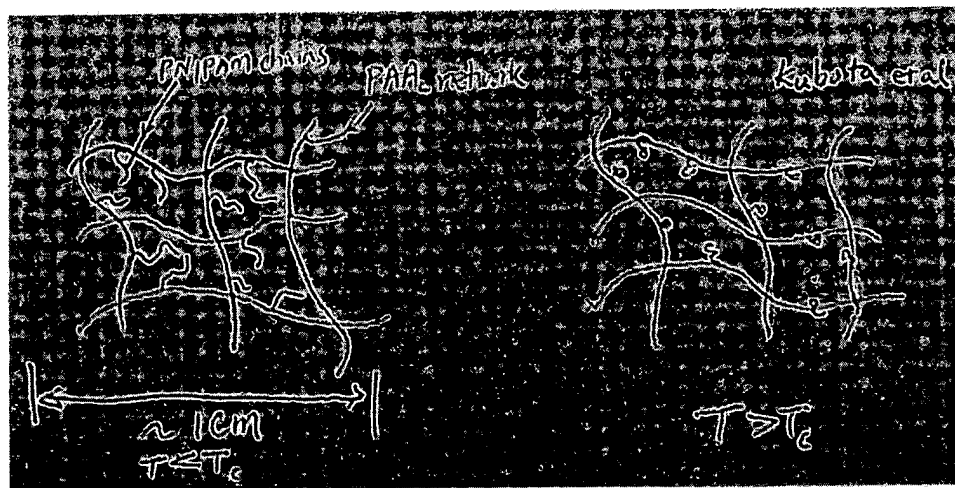
Applicants disagree, since at any temperature, the hydrogel of the Dhara Reference remains as a single piece (please see Schematic 1). In the present invention, millions of IPN nanoparticles with a diameter around 200 nm are sticky together at above 34°C to form a gel but not sticky below 33°C to form a liquid (Schematic 2).

The Examiner states that further motivation is in Kubota et al. who teach the application of stimuli and swelling-controlled hydrogels in drug delivery and the need for gels that can change the release rate of incorporated drugs according to the stimuli.



Schematic 6 shows the structure of the hydrogel of the Kubota Reference. (Page 1033, Figure 9, of the Kubota Reference). PNIPAM chains were grafted on the PAAc network. This is called a grafted network and it is totally different from the interpenetrating polymer network. Furthermore, the hydrogel of the Kubota Reference is a single piece below or above  $T_c$  as shown in Schematic 6. The hydrogels of the Kubota Reference in drug delivery relies on extension or contraction of PNIPAM chains on the PAAc network: when the chains are fully extended at  $T < T_c$ , the drug molecules will be slowed down; when the chains are contracted (Fig. 6b), the drug molecules have more space to move so they can be released faster. This is totally different from the currently-described dispersion of hydrogel nanoparticles.

According to the present invention, an aqueous dispersion of hydrogel nanoparticles is a free-flowing liquid at ambient temperature and becomes a gel at body temperature. This nanoparticle dispersion can be mixed with drugs without chemical reaction at room temperature to form a drug delivery liquid. This liquid could be injected into a body to form *in situ*, a gelled drug depot, to slowly release the drug.



Schematic 6

The Examiner states that a person of ordinary skill in the art would have been motivated to modify the method as taught by Dhara et al. according to the teachings of Gan & Lyon and Hennink & Nostrum to provide an aqueous dispersion of hydrogel nanoparticles and a method of preparing

hydrogel nanoparticles. The motivation as taught by Kubota et al. would be to provide stimuli and swelling-controlled hydrogels that can change the release rate of incorporated drugs according to the stimuli.

Applicants submit that Schematic 3 and 4, with the description above, show totally different sample preparation processes, and that Schematic 1 and 2 show entirely different performances.

Moreover, the hydrogel of the Dhara Reference is a single piece of hydrogel. This piece is not a fluid, and cannot flow at any temperatures. The current invention comprises millions hydrogel nanoparticles are mixed with water. This mixture flows like a liquid at room temperature but becomes a gel at temperatures above 33°C.

As described above, the method steps of the Dhara Reference are not the same or similar to the claimed process. This is illustrated in Schematic 3 and 4, and described in detail above. The hydrogels of the Dhara Reference do not perform the identical function specified in the claims, and do not undergo a reversible gelation in response to a change in stimulus applied. This is illustrated in Schematic 1 and 2, above.

It is scientifically impossible to make hydrogel nanoparticles using a gasket as a spacer, and in fact, the authors of the Dhara Reference did not claim that they had made nanoscaled hydrogels in their paper. Therefore, combining the prior art cannot achieve the claimed invention.

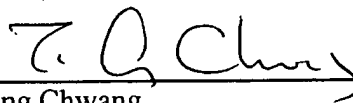
Applicants therefore submit that Claims 1-47 are nonobvious, and patentable under 35 USC §103.

**IV. Conclusion**

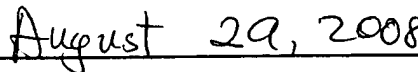
Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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Date